Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update with New Drug Evaluation: Antiepileptics

Date of Review: October 2020

Generic Name: Fenfluramine

Date of Last Review: June 2020
Dates of Literature Search: 02/11/2020 – 7/30/2020
Brand Name (Manufacturer): Fintepla® (Zogenix Inc.)
Dossier Received: Yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To define place in therapy for a new antiepileptic drug (AED) fenfluramine, recently approved by the Food and Drug Administration (FDA) for the treatment of seizures associated with Dravet Syndrome (DS) in patients 2 years of age and older. In addition, new comparative evidence for antiepileptic agents used in management of seizures will be reviewed.

Research Questions:
1. Is there new comparative evidence that AEDs differ in efficacy or harms for management of seizures?
2. What is the effectiveness of fenfluramine in reducing seizures in people with DS?
3. What are the comparative harms of fenfluramine in people with DS?
4. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which fenfluramine may be beneficial or cause more harm?

Conclusions:
- No new publications were identified to provide comparative evidence on the efficacy or harms of AEDs in the management of seizures.
- Two phase 3 clinical trials (Study 1 and Study 2) contribute to the safety and efficacy data of fenfluramine in managing seizures associated with DS.[1,2]
- Study 1 was a multi-center, randomized, double-blind study that compared two doses of fenfluramine (0.2 and 0.7 mg/kg/day) with placebo in children with DS (n=119) aged 2-18 years over 14 weeks.[1] Patients receiving stiripentol were excluded from this study because pharmacokinetic data were not yet available to evaluate dosage modifications for an expected fenfluramine-stiripentol drug interaction.[1] Moderate-quality evidence shows that patients receiving adjunctive fenfluramine 0.7 mg/kg/day experienced a 62.3% (95% CI 47.7 to 72.8) reduction in mean monthly convulsive seizure frequency (MCSF) compared to participants receiving adjunctive placebo ($p<0.0001$).[1] Significant reduction in MCSF was also observed with the fenfluramine 0.2mg/kg/day dose compared to placebo (MCSF difference of 32.4%; 95% CI 6.2 to 51.3; $p=0.021$).[1]

Author: Deanna Moretz, PharmD, BCPS

- Study 2 was similar to Study 1, but used a different dosing regimen because adjunctive stiripentol therapy was permitted in this trial.[2] Fenfluramine 0.4 mg/kg/day was compared with placebo in DS children (n=87) aged 2-18 years over 15 weeks.[2] The 0.4 mg/kg/day dose was used to account for the interaction between fenfluramine and stiripentol and was designed to approximate the fenfluramine 0.7 mg/kg/day dose used in Study 1.[2] Low-quality evidence shows patients receiving adjunctive fenfluramine 0.4 mg/kg/day experienced a 54.0% (95% CI 35.6 to 67.2) greater reduction in mean MCSF compared to those receiving adjunctive placebo ($p<0.001$).[2] Low-quality evidence demonstrates significantly more patients in the fenfluramine group than the placebo group experienced 50% or greater reduction in mean MCSF (54% vs. 5%; $p<0.001$) and a statistically significant duration of longer seizure-free intervals (median [range], 22.0 [3.0-105.0] days vs. 13.0 [1.0-40.0] days; $p=0.004$).[2]
- The most common adverse events reported during fenfluramine treatment at doses of 0.2 mg/kg/day, 0.7 mg/kg/day and 0.4mg/kg/day were decreased appetite (23-49%), diarrhea (15-31%), somnolence (23-26%), fatigue (15-30%), pyrexia (5-21%), and decreased weight (5-13%).[3]
- Fenfluramine is only available through a Risk Evaluation and Mitigation Strategy (REMS) program due to boxed warnings of possible valvular heart disease and pulmonary arterial hypertension occurring with fenfluramine administration.[3] Cardiac monitoring with an echocardiogram is required before, during, and after treatment with fenfluramine.[3] No cases of pulmonary arterial hypertension or valvular heart disease were observed among DS patients who were exposed to fenfluramine in the 2 short-term clinical trials, but trials were not designed or powered to detect these serious adverse events.[1,2]
- Comparative effectiveness of fenfluramine with other AEDs approved for DS has not been evaluated. There is insufficient evidence regarding the long-term safety and efficacy of fenfluramine in DS patients.
- In July 2020, the Food and Drug Administration (FDA) approved cannabidiol oral solution for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients 1 year of age and older.[4] Cannabidiol dosing in TSC patients can be titrated up to 25 mg/kg/day, which differs from the maximum dose of 20 mg/kg/day approved for patients with DS and Lennox-Gastaut Syndrome (LGS).[4] Cannabidiol is now approved to treat seizures associated with DS, LGS, and TSC for patients 1 year of age and older.[4] The previous age range for DS and LGS was 2 years of age and older.

Recommendations:

- Designate fenfluramine as non-preferred with implementation of prior authorization (PA) criteria to ensure medically appropriate utilization on the Oregon Health Plan (OHP) Practitioner-Managed Prescription Drug Plan (PMDP).
- Revise PA criteria for cannabidiol to reflect expanded indication and appropriate dosing for TSC in patients 1 year of age and older.
- Rename AED class name from “oral and rectal” to “non-injectable” to account for nasal formulations.
- Review costs in executive session.
- After executive session, the decision was made to maintain midazolam nasal spray and diazepam nasal spray as non-preferred agents on the PDL.

Summary of Prior Reviews and Current Policy

The AED class of drugs was recently reviewed at the June 2020 Pharmacy and Therapeutics (P&T) Committee meeting. A new AED, cenobamate, approved for treatment of focal seizures was reviewed at this meeting. The P&T Committee designated cenobamate as a non-preferred drug on the OHP PMPDP with PA criteria to ensure medically appropriate utilization. The preferred and non-preferred oral and rectal AEDs included on the Oregon Medicaid FFS (Fee-For-Service) Preferred Drug List (PDL) are listed in **Appendix 1**. Lamotrigine is classified as a voluntary medication due to its utilization in mental health treatment. The utilization of cannabidiol, clobazam, pregabalin, stiripentol, and topiramate is guided by prior authorization (PA) criteria to ensure they are prescribed for indications supported by the medical literature. The PA criteria for specific AEDs are presented in **Appendix 5.**

Medicaid Fee-for-Service Utilization
A review of pharmacy AED claims provided an overview of Medicaid Fee for Service (FFS) utilization in the second quarter of 2020. Ninety-eight percent of the claims were for preferred or voluntary agents in the AED class. The most frequently requested preferred agent was lamotrigine with over 60% of claims, followed by divalproex (23%) and gabapentin (4%). The most requested non-preferred AED was pregabalin followed by clobazam.

Background:
Severe myoclonic epilepsy infancy (SMEI), also known as Dravet syndrome, is a rare genetic epilepsy syndrome characterized by refractory seizures beginning before the age of 1 year with poor neurodevelopmental outcomes and a high mortality rate.[5] It accounts for less than 5% of epilepsy cases presenting in the first year of life, and is estimated to affect 1 in 40,000 live births in the US.[6] Dravet syndrome affects males and females in equal proportions.[7] Mutations in the voltage-gated sodium channel alpha-1 (SCN1A) gene are identified in 70 to 80% of patients with DS.[5] The most common presenting symptom is a hemiclonic or generalized seizure, often precipitated by fever, in an otherwise healthy infant between five and eight months of age.[5] Early seizures tend to be prolonged, recurrent, and may evolve into status epilepticus. Neurodevelopmental decline typically begins shortly after seizure onset. Between one and five years of age, patients with DS have refractory epilepsy characterized by multiple types of seizures, both febrile and afebrile, including convulsive seizures, myoclonic seizures, atypical absence seizures, and focal seizures.[5] Reduction in seizure frequency of 50% or more is generally accepted as demonstrating efficacy for FDA approval of new AEDs.

Drug resistance is a well-recognized feature of seizures in DS, and antiepileptic therapies have overall limited efficacy.[8] Pharmacologic therapy remains the mainstay of treatment.[5] Ketogenic diet and neuromodulation are viable options in selected patients.[5] The goals of treatment are to reduce both the length and number of seizures, prevent status epilepticus, limit adverse effects of antiepileptics to promote better neurocognitive development, and improve quality of life.[5] The most commonly used drugs in patients with DS include valproate, clobazam, topiramate, levetiracetam, and zonisamide.[5] In 2018, stiripentol and cannabidiol received FDA approval for use as adjunctive therapy in DS.[4,9] National Institute for Health and Care Excellence (NICE) 2012 guidance on management of epilepsy recommends valproate and topiramate as first-line agents for treatment of DS.[10] The NICE guidance recommends clobazam and stiripentol as second-line medications to manage DS.[10] Certain AEDs can worsen seizures in patients with DS; these include phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, lamotrigine, vigabatrin, rufinamide, and tiagabine.[5] These medications should avoided when managing seizure associated with DS.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 4 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses),[11,12] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[13] or outcome studied (e.g., non-clinical).[14]

New Guidelines: No new guidelines were identified for this review.

New Indications and Formulations:
1. Cannabidiol Oral Solution: Expanded Indication
In July 2020, the FDA approved cannabidiol oral solution (Epidiolex®) for the treatment of seizures associated with TSC in patients one year of age and older.[4] Tuberous sclerosis complex is a rare genetic disease that causes benign tumors to grow in the brain and other parts of the body, such as the eyes, heart, kidneys, lungs, and skin. It usually affects the central nervous system and can result in a combination of symptoms, including seizures, developmental delay, and behavioral problems.

The efficacy of cannabidiol in managing with seizures associated with TSC was conducted in 224 patients aged 1 to 65 years in a double blind RCT conducted over 16 weeks.[4] The study compared cannabidiol 25 mg/kg/day and 50mg/kg/day with placebo.[4] Most patients were taking 1-2 concomitant AEDs during the trial.[4] The most commonly used concomitant AEDs (greater than 25%) were valproate (45%), vigabatrin (33%), levetiracetam (29%), and clobazam (27%).[4] The baseline median TSC-associated seizure frequency was 57 per 28 days for the combined groups.[4] The primary efficacy measure was the change in seizure frequency of TSC-associated seizures over the 16-week treatment period compared with baseline.[4] The percentage change from baseline (reduction) in the frequency of TSC-associated seizures was significantly greater for patients treated with cannabidiol 25 mg/kg/day than for placebo (-43 vs.-20; $p<0.01$).[4] The most common adverse reactions that occurred in cannabidiol 25 mg/kg/day-treated patients with TSC (incidence at least 10% at the recommended dosage and greater than placebo) were diarrhea; transaminase elevations; decreased appetite; somnolence; pyrexia; and vomiting.[4] The efficacy and safety results for patients treated with cannabidiol 50mg/kg/day were not reported. The maximum recommended daily dose of cannabidiol for seizures associated with TSC is 25 mg/kg/day.[4]

Previously, cannabidiol was approved for the treatment of seizures associated with LGS and DS aged 2 years and older. With the expanded indication for seizures associated with TSC, the minimum age of approved cannabidiol treatment was lowered to 1 year of age for all 3 seizures types by the FDA.[4] The maximum recommended daily dose of cannabidiol to manage seizures associated with LGS and DS is 20mg/kg/day.[4]

2. Midazolam: New Formulation
In May 2019, the FDA approved a new midazolam nasal spray (Nayzilam®). This product is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity in patients with epilepsy 12 years and older.[15] The dose of midazolam nasal spray is 5 mg administered into one nostril.[15] If the patient does not respond to the initial dose, 1 additional spray into the opposite nostril may be administered after 10 minutes.[15] Nayzilam® is supplied in boxes of 2 single-use nasal spray units each contained within an individual blister pack.[15]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[16]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Zonisamide	ZONEGRAN	4/2020	Warnings and Precautions	<u>Acute Myopia and Secondary Angle Closure Glaucoma:</u> Acute myopia and secondary angle closure glaucoma have been reported in patients receiving zonisamide. Elevated intraocular pressure can lead to serious sequelae, including permanent vision loss, if left untreated. Symptoms in reported cases have included acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with ciliochoroidal effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within one month after initiating therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with zonisamide has been reported both in pediatric patients and in adults. The primary treatment to reverse symptoms is discontinuation of zonisamide as rapidly as possible, according to the judgment of the treating physician. Other therapeutic measures, in conjunction with discontinuation of zonisamide, may be helpful. Myopia and secondary angle closure glaucoma usually resolve or improve after discontinuation of zonisamide <u>Hyperammonemia and Encephalopathy:</u> Hyperammonemia and encephalopathy have been reported with the post marketing use of zonisamide. Zonisamide treatment inhibits carbonic anhydrase activity, which may cause metabolic acidosis that is associated with an increased risk for developing hyperammonemia. Hyperammonemia resulting from zonisamide can also be asymptomatic.

				The risks of hyperammonemia and various manifestations of encephalopathy may be increased in patients treated with zonisamide and concomitantly taking other medications that can cause hyperammonemia, including valproic acid or topiramate. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy and this risk may be increased by zonisamide use. Measure serum ammonia concentration if signs or symptoms (e.g., unexplained change in mental status, vomiting, or lethargy) of encephalopathy occur. Hyperammonemia resulting from zonisamide resolves when zonisamide is discontinued. Hyperammonemia from zonisamide may resolve or decrease in severity with a decrease of the daily dose.
Gabapentin Pregabalin	NEURONTIN, HORIZANT LYRICA	4/20 4/20	Warnings and Precautions	<u>Respiratory Depression</u> *(Newly added subsection)* There is evidence from case reports, human studies, and animal studies associating gabapentin and pregabalin with serious, life-threatening, or fatal respiratory depression when co-administered with CNS depressants, including opioids, or in the setting of underlying respiratory impairment. When the decision is made to co-prescribe gabapentin or pregabalin with another CNS depressant, particularly an opioid, or to prescribe gabapentin or pregabalin to patients with underlying respiratory impairment, monitor patients for symptoms of respiratory depression and sedation, and consider initiating therapy at a low dose. The management of respiratory depression may include close observation, supportive measures, and reduction or withdrawal of CNS depressants (including gabapentin or pregabalin).
Topiramate	TOPAMAX	6/20	Warnings and Precautions	<u>Serious Skin Reactions</u> *(Newly added subsection)* Serious skin reactions (Stevens-Johnson Syndrome [SJS] and Toxic Epidermal Necrolysis [TEN]) have been reported in patients receiving topiramate. Topiramate should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. Inform patients about the signs of serious skin reactions.

Randomized Controlled Trials:

A total of 19 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Fenfluramine (Fintepla®)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Fenfluramine, an amphetamine derivative, was initially approved by the FDA in 1973 as an appetite suppressant in adults. It was removed from the United States (U.S.) market in 1997 due to reports of cardiac valve abnormalities and pulmonary arterial hypertension associated with fenfluramine administration at doses of 60 to 120mg per day, with or without phenteramine.[17] Fenfluramine (Fintepla®) oral solution, recently received FDA-approval for the treatment of seizures associated with DS in patients 2 years of age and older.[3] It is a categorized as a Schedule IV controlled substance due to risk of drug abuse and dependence.[3] The initial dose is 0.1 mg/kg twice daily, and can be increased to 0.35 mg/kg twice daily based on efficacy and tolerability for patients not concurrently taking stiripentol.[3] Patients taking concomitant stiripentol plus clobazam should not take more than 0.2 mg/kg of fenfluramine twice daily.[3] Fenfluramine is only available through a REMS program due to boxed warnings of possible valvular heart disease and pulmonary arterial hypertension occurring with fenfluramine therapy. Prior to starting treatment, patients must undergo an echocardiogram to evaluate for valvular heart disease.[3] Echocardiograms should be repeated every 6 months, and once 3 to 6 months post-treatment with fenfluramine.[3]

Two, phase 3 clinical trials (Study 1 and Study 2) contribute to the efficacy data for DS which are described and evaluated below in **Table 3**. The primary efficacy endpoint in the studies was reduction in seizure frequency as measured by change in MCSF from baseline. Study 1 was a multi-center, randomized, double-blind study that compared two doses of fenfluramine (0.2 and 0.7 mg/kg/day) with placebo in DS children (n=119) aged 2-18 years.[1] One hundred seventy three patients were screened for eligibility, of whom 54 patients were ineligible.[1] The two most common reasons for exclusion were the presence of predefined exclusionary cardiovascular or cardiopulmonary findings, primarily trace mitral or trace aortic valve regurgitation during screening echocardiogram exam and failure to meet other entry requirements.[1] After a 6-week period to establish baseline seizure frequency, study participants received fenfluramine or placebo as adjunctive therapy along with their current AED regimen (excluding stiripentol) over a 14-week study period.[1] During the 2-week titration period, patients receiving fenfluramine 0.7 mg/kg/day were first initiated with 0.2 mg/kg/day for 4 days, and then 0.4 mg/kg/day for 4 days before reaching their final dose.[1] All patients were maintained on their final dose for an additional 12 weeks.[1] Patients receiving stiripentol were excluded from this study because pharmacokinetic data were not yet available to evaluate dosage modifications needed to compensate for an expected fenfluramine-stiripentol drug interaction.[1] Enrolled patients with Dravet syndrome were experiencing seizures not completely controlled by their current regimen (mean, 40.3 seizures per 28 days) with stable doses of antiepileptic drugs (valproate, n=71 (60%); clobazam, n=70 (59%); topiramate, n=30 (25%); levetiracetam, n=26 (22%).[1] During treatment, the median reduction in seizure frequency was 74.9% in the fenfluramine 0·7 mg/kg group (from median 20.7 seizures per 28 days to 4.7 seizures per 28 days), 42.3% in the fenfluramine 0.2 mg/kg group (from median 17.5 seizures per 28 days to 12.6 per 28 days), and 19.2% in the placebo group (from median 27.3 per 28 days to 22·0 per 28 days).[1] Those receiving adjunctive fenfluramine 0.7 mg/kg/day experienced a 62.3% (95% CI 47.7 to 72.8%) reduction in mean MCSF compared to participants receiving adjunctive placebo ($p<0.0001$).[1] Significant reduction in MCSF was also observed with the fenfluramine 0.2mg/kg/day dose compared to placebo (difference 32.4%; 95% CI 6.2 to 51.3%; $p=0.021$).[1]

Study 2 was similar to Study 1, but used a different dosing regimen because adjunctive stiripentol therapy was permitted in this trial. A total of 115 patients were screened for eligibility, and 87 patients were randomized to treatment.[2] Most patients who failed screening did not meet the randomization criteria (26 of 28

patients [93%]), including meeting baseline seizure frequency, echocardiogram requirements, and compliance with daily seizure diary; additionally, 1 patient elected to withdraw during screening, and 1 withdrew because of use of a prohibited medication.[2] Of those randomized, 3 in the placebo group and 7 in the fenfluramine group withdrew early due to: adverse event (n=2), protocol deviation (n=1), lack of efficacy (n=1), worsening of seizures (n=1), physician decision (n=1), and patient decision (n=1).[2] Fenfluramine 0.4 mg/kg/day was compared with placebo in DS children (n=87) aged 2-18 years.[2] Participants received fenfluramine as adjunctive therapy along with their current AED regimen over a 15-week study period. Most patients were receiving either 3 concomitant AEDs (placebo group, 26 of 44 [59%]; fenfluramine group, 19 of 43 [44%]) or 4 concomitant AEDs (placebo group, 16 of 44 [36%]; fenfluramine group, 16 of 43 [37%]).[2] Besides the protocol-specified stiripentol, the most frequent AEDs were clobazam (n=82), levetiracetam (n=13), topiramate (n=21), and valproate (n=77).[2] The dose titration period in Study 1 was 2 weeks, while Study 2 used a 3-week dose titration period. Both studies used a 12-week maintenance period to evaluate safety and efficacy of fenfluramine. The 0.4 mg/kg/day dose was used to account for the interaction between fenfluramine and stiripentol and was designed to approximate the fenfluramine 0.7 mg/kg/day dose used in Study 1.[2] Those receiving adjunctive fenfluramine 0.4 mg/kg/day experienced a 54.0% (95% CI 35.6 to 67.2) greater reduction in mean MCSF compared to those receiving adjunctive placebo ($p<0.001$).[2] Significantly more patients in the fenfluramine group than the placebo group experienced 50% or greater reduction in mean MCSF (fenfluramine group, 54% vs. placebo group, 5%; $p<0.001$) and significantly longer seizure-free intervals (median [range], 22.0 [3.0-105.0] days vs. 13.0 [1.0-40.0] days; $p=0.004$).[2]

Study Limitations: Due to the adverse effect profile of fenfluramine (loss of appetite, somnolence, fatigue), it is possible that unblinding may have occurred in patients receiving the active drug in both RCTs. Unblinding may have impacted caregiver reporting of seizure frequency. Both studies were relatively short and there is insufficient evidence regarding the long-term efficacy and safety of fenfluramine. Comparative effectiveness of fenfluramine with other AEDs approved for DS in head-to-head trials has not been evaluated.

Clinical Safety:

The most common adverse events during fenfluramine treatment were decreased appetite, diarrhea, somnolence, fatigue, pyrexia, and decreased weight.[3] Adverse reactions that occurred in 10% or more of patients treated with fenfluramine in the 2 placebo-controlled trials are presented in **Table 1.** No cases of pulmonary arterial hypertension or valvular heart disease were observed among DS patients who were exposed to fenfluramine at doses less than 0.7 mg/kg/day in the 2 short-term clinical trials.[1,2] However, based on prior data, fenfluramine does have a boxed warning regarding the risk of valvular heart disease and pulmonary arterial hypertension.[3] Cardiac monitoring with an echocardiogram is required before, during, and after treatment with fenfluramine.[3] If valvular heart disease or pulmonary arterial hypertension is observed on an echocardiogram, the prescriber must consider the benefits versus the risks of initiating or continuing treatment with fenfluramine.[3]

Table 1. Adverse Reactions in 10% or More of Patients Treated with Fenfluramine and Placebo Over 14 to 15 Weeks[3]

	Fenfluramine Groups			
Adverse Reaction	**0.2 mg/kg/day (n=39)**	**0.7 mg/kg/day (n=40)**	**0.4 mg/kg/day (n=43)**	**Placebo (n=84)**
Decreased appetite	23%	38%	49%	8%
Somnolence, sedation, lethargy	26%	25%	23%	11%
Abnormal echocardiogram	18%	23%	9%	6%
Diarrhea	31%	15%	23%	6%
Constipation	3%	10%	7%	0%

Fatigue, malaise, asthenia	15%	10%	30%	5%
Ataxia, balance disorder, gait disturbance	10%	10%	7%	1%
Increased blood pressure	13%	8%	0%	5%
Drooling	13%	8%	2%	0%
Pyrexia	15%	5%	21%	14%
Upper respiratory infection	21%	5%	7%	10%
Vomiting	10%	5%	5%	8%
Decreased weight	13%	5%	7%	1%
Fall	10%	0%	0%	4%

Drug Interactions

Fenfluramine should not be concomitantly used with, or within 14 days of the administration of monoamine oxidase (MAO) inhibitors because of an increased risk of serotonin syndrome.[3] Concomitant administration of fenfluramine and other drugs that increase serotonin (e.g., selective serotonin-norepinephrine reuptake inhibitors [SNRIs], selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs,] bupropion, triptans, etc.), over-the-counter medications (e.g., dextromethorphan), or herbal supplements (e.g., St. John's Wort) may increase the risk of serotonin syndrome.[3] Fenfluramine dose adjustment is required for patients taking stiripentol plus clobazam.[3] Co-administration of fenfluramine with stiripentol plus clobazam, with or without valproate, increases fenfluramine plasma concentrations and decreases its active metabolite, norfenfluramine, because of the inhibition of the metabolism of fenfluramine.[3] If fenfluramine is co-administered with stiripentol plus clobazam, the maximum daily dosage of fenfluramine is 0.2 mg/kg twice daily (maximum total daily dosage of 17 mg).[3] Fenfluramine co-administration with rifampin or a strong CYP1A2 and CYP2B6 inducer will decrease fenfluramine plasma concentrations.[3] An increase in fenfluramine dosage should be considered when co-administered with rifampin or a strong CYP1A2 and CYP2B6 inducer; however, the maximum daily dosage should not be exceeded.[3] Cyproheptadine and potent 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C serotonin receptor antagonists may decrease the efficacy of fenfluramine.[3] Patients should be monitored with co-administration of these medications.[3]

Antiepileptic drugs (AEDs) increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication.[3] Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.[3] Safety of fenfluramine administration longer than 15 weeks is currently being evaluated in an open-label extension trial of patients enrolled in Study 1 and Study 2.

Look-alike / Sound-alike Error Risk Potential: No other medications have been identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction in seizure frequency (all types)
2) Decreased time between seizures
3) Improved quality of life
4) Serious adverse events

Primary Study Endpoint:

1) Change in mean monthly frequency of convulsive seizures compared to baseline

5) Study withdrawal due to an adverse event

Table 2. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Serotonin modulation by interaction with serotonin transporter proteins which increases extracellular serotonin levels and agonist activity at 5HT- receptors
Oral Bioavailability	68-74%
Distribution and Protein Binding	Volume of distribution: 11.9 L/kg; 50% bound to human plasma proteins
Elimination	90% is excreted in the urine as parent drug and metabolites, less than 5% is found in feces
Half-Life	20 hours, age (2 to 50 years) does not affect pharmacokinetics
Metabolism	75% metabolized to active metabolite, norfenfluramine, primarily by CYP1A, CYP2B6, and CYP2D6. Norfenfluramine is metabolized to inactive metabolites.

Abbreviations: kg=kilogram; L=liters

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Lagae L, et al.[1] Study 1 DB, PC, MC, RCT 14 weeks	1. Fenfluramine 0.2 mg/kg/day 2. Fenfluramine 0.7 mg/kg/day 3. Placebo Current AED regimen continued, stiripentol excluded	Demographics: -Mean age: 9 yrs -Male gender: 54% -Caucasian: 82% -Mean baseline convulsive seizure frequency per month: 40 -Mean number of concomitant AEDs: 2.4 (range 0-5) Key Inclusion Criteria: -DS patients with uncontrolled seizures despite AED therapy aged 2-18 yrs Key Exclusion Criteria: -Any mitral or aortic valve regurgitation -History of pulmonary hypertension -Concurrent serotonergic agents, monoamine oxidase inhibitors or cannabidiol products 21 days before screening	ITT: Total=119 1. 39 2. 40 3. 40 PP: Total=110 1. 39 2. 34 3. 37 Attrition: 1.0 (0%) 2.6 (15%) 3.3 (8%)	Primary Endpoint: Reduction in mean monthly convulsive seizure frequency compared to placebo from baseline: 1 vs. 3: difference = -32.4% (95% CI -6.2 to -52.3) p=0.021 2 vs. 3 difference = -62.3% (95% CI -47.7 to -72.8) p<0.0001 Secondary Endpoints: 1. Median reduction in total seizure frequency per 28 days 1. 42.3% (17.5 to 12.6 seizures) Range = -100 to 197.6 2. 74.9% (20.7 to 4.7 seizures) Range = -100 to 196.4 3. 19.2% (27.3 to 22.0 seizures) Range = -76.1 to 51.8 1 vs. 3 p=0.2035, 95% CI NR 2 vs. 3 p<0.0001, 95% CI NR 2.. Patients with 50% reduction in seizure frequency 1. 15 (38%) 2. 27 (68%) 3. 5 (12%) 1 vs.3: OR 4.8; 95% CI 1.5 to 15.0 p=0.009 2 vs. 3: OR = 15; 95% CI 4.5 to 50.0 p<0.0001 3. Longest seizure-free interval in days (mean) 1. 26 (SD 31.7) 2. 32.9 (SD 27.5) 3. 10.6 (SD 6.0)	32%/4 62%/2 26%/4 56%/2	AEs: 1. 37 (95%) 2. 38 (95%) 3. 26 (65%) SAEs: 1. 4 (10%) 2. 5 (13%) 3. 4 (10%) Decreased Appetite: 1. 8 (20%) 2. 15 (38%) 3. 2 (5%) Fatigue: 1. 4 (10%) 2. 4 (10%) 3. 1 (2%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Assigned 1:1:1 via IWRS stratified across ages (<6 yrs vs. ≥6 yrs) to ensure balance of 25% across treatments. Baseline characteristics balanced across treatment groups. Performance Bias: High. Matched placebo used (identical in appearance and taste). Side effects of fenfluramine may have contributed to unblinding. Detection Bias: Unclear. Fenfluramine and placebo were identical in appearance and taste. Seizures were documented by parents or caregivers in an electronic diary. Attrition Bias: High. Higher percentage of study withdrawals in fenfluramine 0.7mg/kg/day arm due to adverse events. Modified ITT analysis used to analyze all patients who received 1 dose of medication with 1 week of seizure diary data. Missing data were not imputed. Reporting Bias: Low. Protocol available at Lancet website. Outcomes reported as prespecified. Other Bias: High. Funded by Zogenix. Manufacturer provided trial oversight, preparation of drugs and placebo, data monitoring and statistical analysis. Author conflict of interest statements reported in depth. **Applicability**: Patient: Studied in children and young adults, cannot extrapolate results to adults >19 yo or in patients taking stiripentol. Study population did not display extensive diversity (82% Caucasian). Intervention: Dosing based on pharmacokinetic analysis. Comparator: Placebo designed to be administered in same volume as study drug.

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				p-value and 95% CI NR 4. Longest seizure-free interval in days (median [range]) 1. 15 (3 to 106) 2. 25 (2 to 97) 3. 9.5 (2 to 23) 1 vs. 3: Median difference: 4.5 95% CI 0 to 9; P=0.035 2 vs. 3: Median difference: 15.5 95% CI 6 to 25; P=0.0001				Placebo appropriate comparator as subjects continued with current AED regimen. Outcomes: Change in convulsive seizure frequency is an appropriate outcome to assess efficacy. Setting: 55 sites United States n=19 Canada n=2 Western Europe n=27 Japan n=4 Australia n=3
2. Nabbout R, et al.[2] Study 2 DB, PC, MC,RCT 15 weeks	1. Fenfluramine 0.4 mg/kg/day 2. Placebo In addition to current AED regimen, stiripentol required	Demographics: Mean age: 9.1 yrs (SD 4.8 yrs) Male gender: 57% Caucasian: 52% Mean baseline convulsive seizure frequency per month: 25 (range 21 to 28) -Mean number of AEDs: 3 (range 2-5) Key Inclusion Criteria: -DS patients with uncontrolled seizures (≥ 6 seizures during the 6-week baseline) despite stiripentol-inclusive AED therapy aged 2-18 yrs Key Exclusion Criteria: -Any mitral or aortic valve regurgitation -Diagnosis of pulmonary hypertension, history of cardiovascular or cerebrovascular disease	ITT: Total =87 1. 43 2. 44 PP: Total=77 1. 36 2. 41 Attrition: 1. 7 (16%) 2. 3 (7%)	Primary Endpoint: Reduction in monthly mean convulsive seizure frequency compared to placebo from baseline: 1 vs. 2 Difference: 54% 95% CI 35.6 to 67.2 P<0.001 Secondary Endpoints: Patients with 50% reduction in seizure frequency from baseline 1. 23 (54%) 2. 2 (5%) OR 26.0 95% CI 5.5 to 123.2 P<0.001 2. Longest seizure-free interval in days (median range) 1. 22 (3 to 105) 2. 13 (1 to 40) 1 vs. 2 Median difference: 9 95% CI NR p=0.004 3. Longest seizure-free interval in days (mean)	54%/2 49%/3 NA	AEs: 1. 42 (98%) 2. 42 (96%) SAE 1. 6 (14%) 2. 7 (16%) Discontinuations due to AE: 1. 3 (7%) 2. 0 (0%) Decreased Appetite: 1. 19 (44%) 2. 5 (11%) Fatigue: 1. 11 (26%) 2. 2 (5%)		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IWRS stratified across ages (<6 yrs vs. ≥6 yrs) to ensure balance of 40% across treatments. Mean baseline seizure frequency and number of AEDs were balanced across groups. Performance Bias: High. Use of matched placebo. Side effects of active drug could lead to unblinding. Detection Bias: Unclear. Placebo matched to fenfluramine solutions. Caregivers recorded doses, rescue medication, and the number and type of seizures in handheld electronic diaries. Attrition Bias: High. Higher percentage of study withdrawals in fenfluramine arm due to protocol deviation, lack of efficacy, physician or patient decision, and AEs (n=1-2 for each). Modified ITT analysis used to analyze all patients who received 1 dose of medication with 1 week of seizure diary data. Missing data were not imputed. Reporting Bias: Unclear. All prespecified outcomes reported. Protocol available on line. Other Bias: High. Funded by Zogenix, also responsible for design and conduct of the study. Several authors report research support from Zogenix or are employees of the manufacturer. **Applicability**:

		-Concurrent serotonergic agents, monoamine oxidase inhibitors or cannabidiol products 21 days before screening		1. 29.7 (SD 27.3) 2. 13.4 (SD 7.5) Mean Difference =19.9 p value NR				Patient: All patients were taking stiripentol, an AED with proven efficacy in DS. Baseline seizure control slightly better than Study 1. Cannot apply results to patients older than 19 yrs. Intervention: Active drug dosing adjusted to account for drug interaction with concomitantly administered AEDs. Comparator: Placebo appropriate comparator as subjects continued with current AED regimen. Outcomes: Reduction in seizure frequency is an appropriate endpoint. Not all data was reported for primary outcome and secondary outcome of 50% reduction in seizure frequency may be imprecise due to wide CI. Setting: Large number of sites for small population (n=87), potential for inter-site variability with respect to study administration. 32 sites in Canada (n=2) France (n=10) Germany (n=3) Netherlands (n=2) Spain (n=3) United Kingdom (n=5) United States (n=7)
Abbreviations : AED=anti-epileptic drug; AE=adverse event; AED = antiepileptic drug; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; DS = Dravet Syndrome; ITT = intention to treat; IWRS = interactive web response system; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NR = not reported; NNT = number needed to treat; OR = odds ratio; PC = placebo-controlled: PP = per protocol: RCT = randomized clinical trial; SAE = serious adverse event; SD= standard deviation; yrs = years								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
carbamazepine	CARBAMAZEPINE	ORAL	ORAL SUSP	Y
carbamazepine	TEGRETOL	ORAL	ORAL SUSP	Y
carbamazepine	CARBAMAZEPINE	ORAL	TAB CHEW	Y
carbamazepine	CARBAMAZEPINE ER	ORAL	TAB ER 12H	Y
carbamazepine	TEGRETOL XR	ORAL	TAB ER 12H	Y
carbamazepine	CARBAMAZEPINE	ORAL	TABLET	Y
carbamazepine	EPITOL	ORAL	TABLET	Y
carbamazepine	TEGRETOL	ORAL	TABLET	Y
diazepam	DIASTAT	RECTAL	KIT	Y
diazepam	DIASTAT ACUDIAL	RECTAL	KIT	Y
diazepam	DIAZEPAM	RECTAL	KIT	Y
divalproex sodium	DEPAKOTE SPRINKLE	ORAL	CAP DR SPR	Y
divalproex sodium	DIVALPROEX SODIUM	ORAL	CAP DR SPR	Y
divalproex sodium	DEPAKOTE ER	ORAL	TAB ER 24H	Y
divalproex sodium	DIVALPROEX SODIUM ER	ORAL	TAB ER 24H	Y
divalproex sodium	DEPAKOTE	ORAL	TABLET DR	Y
divalproex sodium	DIVALPROEX SODIUM	ORAL	TABLET DR	Y
ethosuximide	ETHOSUXIMIDE	ORAL	CAPSULE	Y
ethosuximide	ZARONTIN	ORAL	CAPSULE	Y
ethosuximide	ETHOSUXIMIDE	ORAL	SOLUTION	Y
ethosuximide	ZARONTIN	ORAL	SOLUTION	Y
ethotoin	PEGANONE	ORAL	TABLET	Y
gabapentin	GABAPENTIN	ORAL	CAPSULE	Y
gabapentin	NEURONTIN	ORAL	CAPSULE	Y
gabapentin	GABAPENTIN	ORAL	TABLET	Y
gabapentin	NEURONTIN	ORAL	TABLET	Y
lacosamide	VIMPAT	ORAL	TABLET	Y
lamotrigine	LAMICTAL	ORAL	TABLET	Y
lamotrigine	LAMOTRIGINE	ORAL	TABLET	Y
lamotrigine	SUBVENITE	ORAL	TABLET	Y
levetiracetam	KEPPRA	ORAL	SOLUTION	Y
levetiracetam	LEVETIRACETAM	ORAL	SOLUTION	Y
levetiracetam	KEPPRA	ORAL	TABLET	Y
levetiracetam	LEVETIRACETAM	ORAL	TABLET	Y
levetiracetam	ROWEEPRA	ORAL	TABLET	Y

methsuximide	CELONTIN	ORAL	CAPSULE	Y
oxcarbazepine	OXCARBAZEPINE	ORAL	ORAL SUSP	Y
oxcarbazepine	TRILEPTAL	ORAL	ORAL SUSP	Y
oxcarbazepine	OXCARBAZEPINE	ORAL	TABLET	Y
oxcarbazepine	TRILEPTAL	ORAL	TABLET	Y
phenobarbital	PHENOBARBITAL	ORAL	ELIXIR	Y
phenobarbital	PHENOBARBITAL	ORAL	TABLET	Y
phenytoin	DILANTIN-125	ORAL	ORAL SUSP	Y
phenytoin	PHENYTOIN	ORAL	ORAL SUSP	Y
phenytoin	DILANTIN	ORAL	TAB CHEW	Y
phenytoin	PHENYTOIN	ORAL	TAB CHEW	Y
phenytoin sodium extended	DILANTIN	ORAL	CAPSULE	Y
phenytoin sodium extended	PHENYTEK	ORAL	CAPSULE	Y
phenytoin sodium extended	PHENYTOIN SODIUM EXTENDED	ORAL	CAPSULE	Y
primidone	MYSOLINE	ORAL	TABLET	Y
primidone	PRIMIDONE	ORAL	TABLET	Y
rufinamide	BANZEL	ORAL	TABLET	Y
tiagabine HCl	GABITRIL	ORAL	TABLET	Y
tiagabine HCl	TIAGABINE HCL	ORAL	TABLET	Y
topiramate	TOPAMAX	ORAL	TABLET	Y
topiramate	TOPIRAMATE	ORAL	TABLET	Y
valproic acid	VALPROIC ACID	ORAL	CAPSULE	Y
valproic acid (as sodium salt)	VALPROIC ACID	ORAL	SOLUTION	Y
zonisamide	ZONISAMIDE	ORAL	CAPSULE	Y
lamotrigine	LAMICTAL (BLUE)	ORAL	TAB DS PK	V
lamotrigine	LAMICTAL (GREEN)	ORAL	TAB DS PK	V
lamotrigine	LAMICTAL (ORANGE)	ORAL	TAB DS PK	V
lamotrigine	LAMOTRIGINE (BLUE)	ORAL	TAB DS PK	V
lamotrigine	LAMOTRIGINE (GREEN)	ORAL	TAB DS PK	V
lamotrigine	LAMOTRIGINE (ORANGE)	ORAL	TAB DS PK	V
lamotrigine	SUBVENITE (BLUE)	ORAL	TAB DS PK	V
lamotrigine	SUBVENITE (GREEN)	ORAL	TAB DS PK	V
lamotrigine	SUBVENITE (ORANGE)	ORAL	TAB DS PK	V
lamotrigine	LAMICTAL XR	ORAL	TAB ER 24	V
lamotrigine	LAMOTRIGINE ER	ORAL	TAB ER 24	V
lamotrigine	LAMICTAL ODT	ORAL	TAB RAPDIS	V
lamotrigine	LAMOTRIGINE ODT	ORAL	TAB RAPDIS	V

lamotrigine	LAMICTAL	ORAL	TB CHW DSP	V
lamotrigine	LAMOTRIGINE	ORAL	TB CHW DSP	V
lamotrigine	LAMICTAL XR (BLUE)	ORAL	TB ER DSPK	V
lamotrigine	LAMICTAL XR (GREEN)	ORAL	TB ER DSPK	V
lamotrigine	LAMICTAL XR (ORANGE)	ORAL	TB ER DSPK	V
lamotrigine	LAMICTAL ODT (BLUE)	ORAL	TB RD DSPK	V
lamotrigine	LAMICTAL ODT (GREEN)	ORAL	TB RD DSPK	V
lamotrigine	LAMICTAL ODT (ORANGE)	ORAL	TB RD DSPK	V
lamotrigine	LAMOTRIGINE ODT (BLUE)	ORAL	TB RD DSPK	V
lamotrigine	LAMOTRIGINE ODT (GREEN)	ORAL	TB RD DSPK	V
lamotrigine	LAMOTRIGINE ODT (ORANGE)	ORAL	TB RD DSPK	V
brivaracetam	BRIVIACT	ORAL	SOLUTION	N
brivaracetam	BRIVIACT	ORAL	TABLET	N
cannabidiol (CBD)	EPIDIOLEX	ORAL	SOLUTION	N
carbamazepine	CARBAMAZEPINE ER	ORAL	CPMP 12HR	N
carbamazepine	CARBATROL	ORAL	CPMP 12HR	N
cenobamate	XCOPRI	ORAL	TAB DS PK	N
cenobamate	XCOPRI	ORAL	TABLET	N
clobazam	SYMPAZAN	ORAL	FILM	N
clobazam	CLOBAZAM	ORAL	ORAL SUSP	N
clobazam	ONFI	ORAL	ORAL SUSP	N
clobazam	CLOBAZAM	ORAL	TABLET	N
clobazam	ONFI	ORAL	TABLET	N
diazepam	VALTOCO	NASAL	SPRAY	N
eslicarbazepine acetate	APTIOM	ORAL	TABLET	N
felbamate	FELBAMATE	ORAL	ORAL SUSP	N
felbamate	FELBATOL	ORAL	ORAL SUSP	N
felbamate	FELBAMATE	ORAL	TABLET	N
felbamate	FELBATOL	ORAL	TABLET	N
fenfluramine HCl	FINTEPLA	ORAL	SOLUTION	N
gabapentin	GABAPENTIN	ORAL	SOLUTION	N
gabapentin	NEURONTIN	ORAL	SOLUTION	N
gabapentin	GRALISE	ORAL	TAB ER 24H	N
gabapentin enacarbil	HORIZANT	ORAL	TABLET ER	N
lacosamide	VIMPAT	ORAL	SOLUTION	N
lacosamide	VIMPAT	ORAL	TAB DS PK	N
levetiracetam	KEPPRA XR	ORAL	TAB ER 24H	N
levetiracetam	LEVETIRACETAM ER	ORAL	TAB ER 24H	N

levetiracetam	SPRITAM	ORAL	TAB SUSP	N
midazolam	NAYZILAM	NASAL	SPRAY	N
oxcarbazepine	OXTELLAR XR	ORAL	TAB ER 24H	N
perampanel	FYCOMPA	ORAL	ORAL SUSP	N
perampanel	FYCOMPA	ORAL	TABLET	N
pregabalin	LYRICA	ORAL	CAPSULE	N
pregabalin	PREGABALIN	ORAL	CAPSULE	N
pregabalin	LYRICA	ORAL	SOLUTION	N
pregabalin	PREGABALIN	ORAL	SOLUTION	N
rufinamide	BANZEL	ORAL	ORAL SUSP	N
stiripentol	DIACOMIT	ORAL	CAPSULE	N
stiripentol	DIACOMIT	ORAL	POWD PACK	N
topiramate	TROKENDI XR	ORAL	CAP ER 24H	N
topiramate	QUDEXY XR	ORAL	CAP SPR 24	N
topiramate	TOPIRAMATE ER	ORAL	CAP SPR 24	N
topiramate	TOPAMAX	ORAL	CAP SPRINK	N
topiramate	TOPIRAMATE	ORAL	CAP SPRINK	N
vigabatrin	SABRIL	ORAL	POWD PACK	N
vigabatrin	VIGABATRIN	ORAL	POWD PACK	N
vigabatrin	VIGADRONE	ORAL	POWD PACK	N
vigabatrin	SABRIL	ORAL	TABLET	N
vigabatrin	VIGABATRIN	ORAL	TABLET	N
carbamazepine	EQUETRO	ORAL	CPMP 12HR	
phenobarbital	PHENOBARBITAL	ORAL	ELIXIR	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 3 2020, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 31, 2020

1	Carbamazepine	6302
2	Diazepam/	4818
3	divalproex.mp. or Valproic Acid/	8922
4	Ethosuximide/	298
5	ethotoin.mp.	2
6	lacosamide.mp.	840
7	lamotrigine.mp.	5211
8	levetiracetam.mp.	3853
9	methsuximide.mp.	20
10	oxcarbazepine.mp.	1840
11	Phenobarbital/	3185
12	Phenytoin/	3480
14	Primidone/	167
14	rufinamide.mp.	259
15	tiagabine.mp.	879
16	topiramate.mp.	4787
17	Valproic Acid/	8633
18	zonisamide.mp.	1253
19	brivaracetam.mp.	254
20	clobazam.mp.	655
21	esclicarbazepine.mp.	2
22	felbamate.mp.	518
23	perampanel.mp.	475
24	Pregabalin/	1925
25	Vigabatrin/	1066
26	Gabapentin	3533
27	midazolam spray.mp	13
28	stiripentol.mp	209
29	Cannabidiol/	1257
30	cenobamate.mp	16
31	Fenfluramine	1152
32	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31:	44645
33	Epilepsy/	42396
34	32 and 33	6136

34 limit 29 to (english language and humans and yr="2018 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 19

Author: Moretz

Date: October 2020

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FINTEPLA safely and effectively. See full prescribing information for FINTEPLA.

FINTEPLA® (fenfluramine) oral solution, CIV
Initial U.S. Approval: 1973

WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION
See full prescribing information for complete boxed warning.

- **There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension. (5.1, 5.2)**
- **Echocardiogram assessments are required before, during, and after treatment with FINTEPLA. (2.1, 2.4, 5.1, 5.2)**
- **FINTEPLA is available only through a restricted program called the FINTEPLA REMS. (5.3)**

----------**INDICATIONS AND USAGE**----------
FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. (1)

----------**DOSAGE AND ADMINISTRATION**----------
- FINTEPLA is to be administered orally and may be taken with or without food. (2.2)
- The initial starting and maintenance dosage is 0.1 mg/kg twice daily, which can be increased weekly based on efficacy and tolerability. (2.2)
- Patients not on concomitant stiripentol: The maximum daily maintenance dosage of FINTEPLA is 0.35 mg/kg twice daily (maximum daily dosage of 26 mg). (2.2)
- Patients taking concomitant stiripentol plus clobazam: The maximum daily maintenance dosage of FINTEPLA for patients taking these medications is 0.2 mg/kg twice daily (maximum daily dosage of 17 mg). (2.2)

----------**DOSAGE FORMS AND STRENGTHS**----------
Oral solution: 2.2 mg/mL fenfluramine (3)

----------**CONTRAINDICATIONS**----------
- Hypersensitivity to fenfluramine or any of the excipients in FINTEPLA (4)
- Within 14 days of the administration of monoamine oxidase inhibitors due to an increased risk of serotonin syndrome (4)

----------**WARNINGS AND PRECAUTIONS**----------
- Decreased Appetite and Decreased Weight: Advise patients that FINTEPLA can cause decreased appetite and decreased weight. (5.4)
- Somnolence, Sedation, and Lethargy: Monitor for somnolence and sedation. Advise patients not to drive or operate machinery until they have gained sufficient experience on FINTEPLA. (5.5)
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts. (5.6)
- Withdrawal of Antiepileptic Drugs: FINTEPLA should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus. (5.7)
- Serotonin Syndrome: Advise patients that serotonin syndrome is a potentially life-threatening condition and may occur with FINTEPLA, particularly with concomitant administration of FINTEPLA with other serotonergic drugs. (5.8)
- Increase in Blood Pressure: Monitor blood pressure during treatment. (5.9)
- Glaucoma: Discontinue therapy in patients with acute decrease in visual acuity or ocular pain. (5.10)

----------**ADVERSE REACTIONS**----------
The most common adverse reactions (incidence at least 10% and greater than placebo) were decreased appetite; somnolence, sedation, lethargy; diarrhea; constipation; abnormal echocardiogram; fatigue, malaise, asthenia; ataxia, balance disorder, gait disturbance; blood pressure increased; drooling, salivary hypersecretion; pyrexia; upper respiratory tract infection; vomiting; decreased weight; fall; status epilepticus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zogenix Inc. at 1-866-964-3649 (1-866-Zogenix) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------**DRUG INTERACTIONS**----------
- Dose adjustment is required for patients taking stiripentol plus clobazam. (2.2, 2.3, 7.1)
- Strong CYP1A2 and CYP2B6 Inducers: Coadministration with rifampin or a strong CYP1A2 and CYP2B6 inducer will decrease fenfluramine plasma concentrations. Consider an increase in FINTEPLA dosage when coadministered with rifampin or a strong CYP1A2 and CYP2B6 inducer. (7.1)

----------**USE IN SPECIFIC POPULATIONS**----------
- Administration to patients with moderate or severe renal impairment is not recommended. (8.6)
- Administration to patients with hepatic impairment is not recommended. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2020

Author: Moretz

Date: October 2020

Appendix 4: Key Inclusion Criteria

Population	People with seizures
Intervention	Anti-epileptic therapy
Comparator	Placebo
Outcomes	Reduction in mean convulsive seizure frequency per month
Timing	12 week maintenance period
Setting	United States, Canada, Western Europe, Japan, and Australia

Appendix 5: Prior Authorization Criteria

Cannabidiol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Cannabidiol

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication AND is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Go to #5 Document current seizure frequency_____	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the prescribed dose greater than 25 mg/kg/day?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No**: Go to # 6
6. Are baseline liver function tests (LFTs) on file (serum transaminases and total bilirubin levels)? AND If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1? LFTs should be obtained at 1 month, 3 months, and 6 months after starting treatment with cannabidiol and periodically thereafter as clinically indicated, after cannabidiol dose changes, or addition of other medications that are known to impact the liver.	**Yes:** Approve for 12 months Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent LFT's documented in patient records? AND If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1?	**Yes:** Go to # 2 Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Go to #3 Document baseline and current seizure frequency_____	**No:** Pass to RPh. Deny for lack of treatment response.
3. Is the prescribed dose greater than 25mg/kg/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 4
4. Is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Table 1: Dose Adjustments of Cannabidiol in Patients with Hepatic Impairment[1]

Hepatic Impairment	Starting Dosage	Maintenance Dosage Range in Patients with Lennox-Gastaut Syndrome (LGS) or Dravet Syndrome (DS)	Maintenance Dosage in Patients with Tuberous Sclerosis Complex (TSC)
Mild	2.5 mg/kg twice daily (5 mg/kg/day)	5 to 10 mg/kg twice daily (10 to 20 mg/kg/day)	12.5 mg/kg twice daily (25 mg/kg/day)
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 to 5 mg/kg twice daily (5 to 10 mg/kg/day)	6.25 mg/kg twice daily (12.5 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 to 2 mg/kg twice daily (2 to 4 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)

1. Epidolex (cannabidiol) Oral Solution Prescribing Information. Carlsbad, CA; Greenwich Biosciences, Inc. July 2020.

P&T/DUR Review: 10/20 (DM); 6/2020 (DM); 3/19; 1/19 (DM)
Implementation: 11/1/20; 5/1/19; 3/1/19

Clobazam

Goal(s): To ensure appropriate drug use and restrict to indications supported by medical literature and funded by Oregon Health Plan.

Length of Authorization:
- 12 months

Requires PA:
Clobazam

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have a diagnosis of Lennox-Gastaut syndrome and is the patient 2 years of age or older?	**Yes:** Go to #3	**No:** Go to # 5
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have a diagnosis of Dravet Syndrome and is the patient 2 years of age or older?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

Limitations of Use:

- Clobazam is not FDA-approved for epilepsy syndromes other than Lennox-Gastaut.
- National Institute for Health and Care Excellence (NICE) guidance recommends clobazam as a second line agent for management of Dravet Syndrome.[1]

1. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. nice.org.uk/guidance/cg137. Accessed July 30, 2018

P&T Review: *10/20 (DM); 6/2020 (DM); 1/19 (DM); 3/18; 7/16; 3/15; 5/12*
Implementation: *11/1/20; 3/1/19; 8/16, 8/12*

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin and pregabalin extended release

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for pregabalin?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is the request for pregabalin immediate release?	**Yes:** Go to #4	**No:** Go to #5
4. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to #5

Approval Criteria		
5. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; not funded by the OHP.
6. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of gabapentin for 90 days

Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X
Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	
Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	

Non-funded		
Fibromyalgia	X	

P&T Review: *10/20 (DM); 1/19 (DM); 7/18; 3/18; 3/17*
Implementation: *11/1/20; 10/1/18; 8/15/18; 4/1/17*

Stiripentol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature and funded by Oregon Health Plan.

Length of Authorization:

- Up to 12 months

Requires PA:

- Stiripentol capsules and powder for oral suspension

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for the FDA approved indication of Dravet syndrome in patients 2 years of age and older taking clobazam?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is baseline white blood cell (WBC) and platelet counts on file within the past 3 months? Note: Labs should be assessed every six months while receiving stiripentol therapy.	**Yes:** Approve for 12 months Document results here: Date of lab work_____ WBC_____ Platelets_____	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent WBC and platelet counts documented in patient records? Note: Labs should be assessed every six months while receiving stiripentol therapy.	**Yes:** Go to # 2 Document results here: Date of lab work_____ WBC_____ Platelets_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

P&T/DUR Review: 10/20 (DM); 6/2020 (DM); 1/19 (DM)
Implementation: 11/1/20;3/1/2019

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Non-preferred topiramate products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime.	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #7
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: “Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal.”	

P&T Review: *10/20 (DM); 6/2020 (DM); 5/19 (KS); 1/19 (DM); 7/18; 3/18; 3/17; 7/16; 3/15; 2/12; 9/07; 11/07*
Implementation: *11/1/20; 4/18/15; 5/12, 1/12*

Fenfluramine

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Fenfluramine

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Does the patient have uncontrolled seizures on current baseline therapy with at least one other antiepileptic medication AND is fenfluramine intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Go to #5 Document seizure frequency_____	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the prescribed dose greater than 0.7 mg/kg/day or 26 mg/day OR 0.2 mg/kg/day or 17 mg/day in patients taking stiripentol plus clobazam?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No**: Go to # 6
6. Is baseline echocardiogram on file that was performed within past 6 months?	**Yes:** Approve for 12 months Document results here: Date of echocardiogram_____ Results_____	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has an echocardiogram been obtained within the past 6 months?	**Yes:** Go to # 2 Document results here: Date of echocardiogram____	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Go to #3 Document baseline and current seizure frequency_____	**No:** Pass to RPh. Deny for lack of treatment response.
3. Is the prescribed dose greater than 0.7mg/kg/day or 26 mg/day or greater than 0.2 mg/kg/day or 17 mg/day in patients taking stiripentol plus clobazam?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 4
4. Is fenfluramine prescribed as adjuvant therapy and is patient adherent to all prescribed seizure medications?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *10/2020 (DM)*
Implementation: *11/1/20*